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and Their Genetic Determinants: A Study Within the
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13. ABSTRACT (Maximum 200 Words)

Purpose and scope: we are conducting a large case-control study, nested within a prospective cohort, to estimate relative risks of breast cancer by levels of IGF-I and IGFBP-3, and to examine associations of IGF-I levels and cancer risk with polymorphic variations in a series of 15 candidate genes known to be implicated in the regulation of IGF-I synthesis.

Progress report: In this first year of the project, cases and matched control subjects have been identified, their blood samples (serum and buffy coats) were retrieved from a large biorepository, DNA was extracted from buffy coats, and serum IGF-I and IGFBP-3 were measured. A comprehensive catalogue of single nucleotide polymorphisms (SNPs) in 15 candidate genes was made, by searching databases and by denaturing high-performance chromatography (DHPLC) in our laboratories. Seventy-eight of these SNPs were typed in a cross-sectional sample of subjects, to describe allele and haplotype frequencies. Preliminary statistical analyses, relating the polymorphisms to levels of IGF-I, indicated a subset of 27 polymorphisms that are to be typed with greatest priority in our full study, of 1050 breast cancer cases and 2100 controls.

Major findings: First reportable findings are the complete catalogue of SNPs in our list of candidate genes.

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Introduction

IGF-I is a central hormone in the regulation of anabolic (growth) processes as a function of available energy and elementary substrates (e.g., essential amino acids), and has strongly mitogenic and anti-apoptotic activities. Results from *in vitro* studies and animal experiments show that, in excess, the anabolic signals by IGF-I can promote the development of tumors at various organ sites, and recent epidemiological studies have shown an increased breast cancer risk in women with elevated serum IGF-I, or with elevated levels of IGF-I for given levels of IGFBP-3, the major plasmatic IGF-binding protein.

While nutritional status is one important determinant of circulating IGF-I levels (Kaaks & Lukanova, 2001), heritability studies have shown that, in well-nourished populations, a large part (40-60 %) of variation in IGF-I is (co) determined by genetic factors (Hong et al. 1996; Harrela et al., 1996; Verhaeghe et al., 1996). To increase understanding of what are the major determinants of IGF-I levels, as well as cancer risk, we conduct a study with the following objectives:

1. confirm that elevated prediagnostic serum levels of IGF-I increase breast cancer risk, especially in premenopausal women;
2. describe exhaustively existing polymorphisms, allele frequencies and haplotypes in 15 selected genes related to the secretion of growth hormone, and hence to the synthesis of IGF-I and IGFBP-3; and
3. examine whether these genetic polymorphisms are related to significant increases or decreases in circulating levels of IGF-I and IGFBP-3, as well as in breast cancer risk.

Our project is a large case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), using prediagnostic blood (serum and DNA) samples collected during 1992-1998, from 233,800 women in western Europe.

As mentioned in our original application, the study was planned in four parts:

1. A case-control study (about 1000 cases and 1000 controls) nested in a prospective cohort, to estimate the associations of serum IGF-I and IGFBP-3 levels with breast cancer risk;
2. Preparation of an exhaustive catalog of polymorphisms and haplotypes in the 15 selected candidate genes, and a ("phase-1") association study on a subset of 400 controls to identify genotypes that have a minimum level of association with serum of IGF-I and IGFBP-3;
3. A nested case-control study, to estimate relative risks of breast cancer in relation only to those genotypes selected in phase-1;
4. A ("phase-2") study of associations of these selected genotypes with IGF-I and IGFBP-3, in all cases and controls.

Body

For **year 1**, our workplan (as in the "Statement of Work" section of our application), was as follows:

1. Selection of cases and controls, using the established eligibility and matching criteria, and extraction of case-control data sets with relevant information from questionnaires and anthropometry: **Task 1, months 1-2.**
2. Retrieval of serum and buffy coat samples from the central EPIC storage facility; assembly of the serum samples into batches of matched case-control sets for immunoassays; assembly of the buffy-coat samples into batches for DNA extraction: **Task 2, months 2-4.**
3. Assays of IGF-I and IGFBP-3 serum of breast cancer cases ($n = 1000$) and controls ($n = 1000$): **Task 3, months 7-12.**
4. DNA extraction for all 2000 cases and controls: **Task 5, months 1-12.**
5. Preparation of an exhaustive catalog of polymorphisms by searching the literature, and by DHPLC analysis of DNA from a subset of 200 subjects: **Task 6: months 1-12.**

These goals were mostly met entirely:

- **Task 1:** In October 2001, there were a total of 1852 cases of breast cancer diagnosed after donation of a blood sample. Of these, 1180 had complete information about exogenous hormone use and menopausal status at the time of blood donation. Among the 1180 cases with complete information, we identified 810 cases with breast cancer who did not use any hormones at the time of blood sampling, and for each of these 810 women we selected two control subjects among all women free of cancer until the date of diagnosis of the index case, not using exogenous hormones at the time of blood donation. The control subjects were matched to the cases on study (recruitment) center, and age and date of blood collection, menopausal status, day of the menstrual cycle (in premenopausal women), and fasting status (time since last consumption of food or drinks). For 430 cases (women recruited in the study centres of Naples, Turin, Oviedo, and a number of cities in France), the information on exogenous hormone use was not yet complete in our central database at IARC (some data from a blood collection form still had to be transferred). From amongst these women, an additional 250 cases are expected to be added to the study, by the end of 2002, and to these about 500 control subjects will be matched.
- **Task 2:** For all 810 breast cancer cases selected for the study, and for 1610 matched control subjects, serum and buffy coat samples were retrieved from 30 different liquid nitrogen containers, and regrouped. Samples were put together in batches for hormone (IGF-I and IGFBP-3) assays, and buffy coats were set aside for DNA extraction.
- **Task 3:** IGF-I and IGFBP-3 were measured for 803 cases and for 1560 controls. Further assays are planned, before the end of 2003, for some 250 cases still to be added to the study (as described above), plus their matched controls.
- **Task 5:** DNA has been extracted from the buffy coat samples of 1079 controls and 600 cases (August 2002), and the extraction is currently (September 2002) being completed for the full project of around 1050 cases and 2100 controls. Extracted DNA samples (high concentration) have been out into deep-well microplates; from these, a series of secondary plates, at a lower and standardized

DNA concentration, are being prepared. The secondary plates will be used for the preparation of PCR plates for genotyping (years 2 and 3 of the project).

- **Task 6:** As a first step, we made an exhaustive catalog of polymorphisms (coding and non-coding regions), using a search of literature (MEDLINE) and publicly available databases, as well as experimental discovery using denaturing HPLC (DHPLC), a technology available in our laboratory (Dr Canzian, Genome Analysis Group, IARC). DNA samples of 192 healthy control subjects were used for the discovery of polymorphisms by DHPLC, including 137 Caucasians (from Sweden, Estonia, Germany, Romania, Spain, Basque country and Greece), 43 Africans and 12 Japanese. SNP searches through literature, databases and DHPLC led us to complete a catalogue of 127 polymorphisms.

After the SNP discovery step, we selected polymorphisms of interest for the study, on the basis of allelic frequencies and/or knowledge about a possible functional role. A DNA microarray ("IGF chip") was designed, for a total of 78 SNPs in our list of candidate genes (**Table 1**).

Table 1.

Gene	Number of SNPs on chip	Number of SNP that passed Q.C. ^{a)}	Number of SNPs suitable for haplotyping ^{b)}
GH1	9	5	2
GHR	8	7	3
GHRL	4	3	3
GHRH	2	2	2
GHRHR	10	10	9
IGF1	7	6	4
IGF1R	2	2	2
IGFBP1	4	4	4
IGFBP3	8	6	5
POU1F1	3	2	1
SST	1	1	1
SSTR1	1	1	1
SSTR3	8	8	6
SSTR4	5	4	4
SSTR5	5	5	4
IGFALS	1	0	0
Total	78	66	51

- a) SNPs that could be typed reliably with the chip technology. The criteria for quality control were that the three genotype classes (homozygote for the common allele, heterozygote, homozygote for the rare allele) should be observed and that they should be in Hardy-Weinberg equilibrium
- b) SNPs were considered suitable for haplotyping if they passed quality control and had frequency of the rare allele >5% in this population.

Workplan for year 2,

During year 1, we have been able to start already with some of the work originally scheduled for year 2. The workplan for year 2, as stated in our original proposal includes:

6. Complete genotyping of a subset of 400 controls; Statistical analysis of a phase-1 association study, relating genotypes to serum concentrations of IGF-I and IGFBP-3: **Task 7 in our original workplan, months 12-24;**

After the SNP discovery step (task nr 6, described above) we selected polymorphisms of interest for the study, on the basis of allelic frequencies and/or knowledge about a possible functional role. A DNA microarray ("IGF chip") was designed, for a total of 78 SNPs in our list candidate genes. This microarray was then used to type these SNPs in a cross-sectional study population of 249 women and 228 men [men were also typed, as their DNA was readily available in extracted form, and because allele frequencies and genetic haplotypes are the same in men and women (none of our candidate genes are X-linked)]. In the same cross-sectional study we also measured IGF-I and IGFBP-3, so that we could perform a first analysis of associations of polymorphisms with these two hormonal parameters.

Table 2 shows results of this cross-sectional study, which was used to describe SNP allele frequencies and SNP haplotypes in this sub-population of EPIC. For a number of SNPs, the quality of measurement was insufficient, while for others (initially identified from public database without good prevalence data) we found that the prevalence was very low ($< 1\%$) in our study population. Furthermore, a few SNPs were in close to perfect linkage disequilibrium ($\Delta > 0.90$) with others. After elimination of these various non-informative SNPs, a total of 51 SNPs remained for estimation of major haplotypes, and for statistical analyses of association with IGF-I and IGFBP-3 levels. Haplotypes at the individual level were predicted with custom software prepared by us (Cox et al., manuscript submitted).

We performed preliminary statistical analyses of associations of SNPs, or their combinations into haplotypes, with serum IGF-I and IGFBP-3.

At the level of gene loci, a first approach to assess associations of SNPs with IGF-I and/or IGFBP-3 levels was to estimate the maximum percent of variation in these peptides that could be explained by the individuals' combinations of haplotypes on the two chromosomes (i.e., multi-allelic genotypes, where each haplotype represents a specific allele type) (**Table 2**).

In subsequent steps we refined the analyses, to examine which reduced sets of SNPs could explain most of this variation, using an approach recently described by Cordell and Clayton (2001). This method uses stepwise regression procedures (forward selection and backward elimination strategies), to evaluate the relative importance of different SNP variants, alone or in variable combinations, within a gene. Main effects, as well as their possible interactions, are evaluated for dummy variables representing phased SNP genotypes within each gene locus, where the (parental) phase indicates whether or not different SNP alleles occur together on the same chromosome. By including interaction terms between the SNP genotype variables, it is possible to assess the effects of reduced haplotypes within a gene, composed of minimum sets of SNPs that lead to significant prediction of plasma peptide levels or disease risk. This preliminary analysis helped us select 27 SNPs out of the total of 51) for which associations with IGF-I and / or IGFBP-3 were most likely.

The results from the more refined analyses (**Table 2**) provide preliminary evidence that circulating levels of IGF-I may be associated with polymorphic variation in several genes in the GH/IGF-I pathway, including *IGF1*, *IGFBP3*, *GHR*, *GHRH*, *GHRHR*, *SSTR3* and *GHRL*. The genes *SST*, *SSTR1*, *POU1F1* and *GHSR* were found

to be relatively monomorphic (only one SNP remained for analyses), and only in the *GHSR* gene did one polymorphism show a significant association with levels of IGF-I and IGFBP-3.

With current numbers of observations, associations observed were only of borderline statistical significance, and effects of individual SNP variants on levels of IGF-I or IGFBP-3 were always relatively small. Nevertheless, selected SNPs explained some 20 percent of the total between-subject variation in IGF-I levels. This would correspond to about 40% of the genetically determined variation, if one assumes that an approximate 50% of the total variation is due to heritable factors, as indicated by twin studies.

A larger cross-sectional study will be needed to allow the estimation of such multigenic prediction score with sufficient precision. In year 2, the number of women in the cross-sectional analysis will be increased, and preliminary studies will be extended according to the plans in our initial proposal, for a selected series of 15-25 SNPs. This full study, of all 1050 breast cancer cases plus their matched controls, will allow a much more precise and statistically powerful analysis of associations with both IGF-I levels and breast cancer risk.

Table 2. Plasma IGF-I and IGFBP-3 in relation to polymorphic variation in candidate genes, among 477 men and women in Northern Sweden.

Gene	Number of different alleles		R ² of full rank ("maximum") haplotype model ^{b)}		Result from stepwise regression: ^{c)} Nr of SNP loci showing effects / model p-value / model R ²	
	SNPs ^{a)}	Haplotypes	IGF-I	BP-3	IGF-I	BP-3
IGF1	4	6	0.04	0.03	2 / p = 0.10 / R ² = 0.03	
IGFBP3	5	13	0.09	0.06	2 / p = 0.02 / R ² = 0.05	
GHI	3	4	0.01	0.02		
GHR	5	7	0.05	0.02	1 / p = 0.06 / R ² = 0.02	1 / p = 0.03 / R ² = 0.01
GHRH	2	3	0.02	0.01	1 / p = 0.06 / R ² = 0.02	
GHRHR	10	15	0.10	0.13	1 / p = 0.07 / R ² = 0.02	
SST	1	NA	0.01	0.01		
SSTR1	1	NA	0.004	0.002		
SSTR3	6	12	0.06	0.04	3 / p = 0.06 / R ² = 0.05	
SSTR4	4	9	0.05	0.03		
SSTR5	4	9	0.03	0.02		2 / p = 0.09 / R ² = 0.01
POU1F1	1	NA	0.002	0.001		
GHRL	4	9	0.08	0.06	2 / p = 0.07 / R ² = 0.05	
GHSR	1	NA	0.02	0.02	1 / p = 0.01 / R ² = 0.02	1 / p = 0.07 / R ² = 0.02
IGF1R ^{d)}	2	3	NA ^{d)}	0.01	NA ^{d)}	
IGFBP1 ^{d)}	4	9	NA ^{d)}	NA ^{d)}	NA ^{d)}	NA ^{d)}

^{a)} SNP alleles with frequency below 1% are not counted. ^{b)} Percent of variation in plasma peptide levels explained by a full-rank model including all haplotype combinations on the individuals' two chromosomes (i.e., individuals' multi-allelic genotypes at a gene locus). ^{c)} Number of SNP loci within each gene that predict variation in peptide levels, either as main effect or in interaction with other SNPs; model obtained by stepwise procedures based on a combination of forward selection ($p_{IN} < 0.15$) and backward elimination ($p_{OUT} \geq 0.15$), using phased SNP genotypes. ^{d)} Genes for which a direct association with levels of IGF-I or IGFBP-3 is physiologically less plausible. NA = "not applicable".

Key Research Accomplishments

Key accomplishments in year 1 were:

- an almost full selection of cases and controls within the EPIC cohorts, for the nested case-control study on serum IGF-I, IGFBP-3 and breast cancer risk; a smaller number of cases and controls is being added to the study, so as to reach the full target study size.
- Measurement of IGF-I and IGFBP-3 for the cases and controls
- Close-to complete DNA extraction for the cases and controls (being finalized in September-October 2002)
- Identification of a comprehensive catalog of SNPs in the candidate genes included in the present study
- Preparation of DNA genotyping chip, for 78 of these polymorphisms
- A first descriptive study of SNP and haplotype frequencies for all candidate genes
- A first analysis of associations of SNPs an circulating levels of IGF-I and IGFBP-3.

Reportable Outcomes

A first report documenting SNPs identified in our list of candidate genes is in preparation.

Conclusions

Our study has started without problems, and is fully on schedule. Preliminary results suggest that an important part of between-subject variation in circulating IGF-I levels may be due to polymorphic variations in our list of candidate genes; the planned extension of our study to a larger number of women (breast cancer cases and controls) is needed to confirm this.

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Appendix

Catalogue of polymorphisms found by literature searches and experimentally in the 15 candidate genes.

Gene	Genbank	position	Alle Freq (Caucasians)	Alle freq (Africans)	Alle freq (Japanese)	Alle freq (total)	SNP	Position in gene	Amino acid	Flanking sequence	Codon number
POU1F1	D12887	331	9.42%	2.38%	0.00%	0.08	C/T	Promoter	Non-coding	gtttcaaatgttgattcctctctaaaggctgaactactgaagttgtcacaataa ggttcagatttccctccctccatctatataccccagaaatcagcttctctcggcc atggattatgttgggtaaaaaagagacgggtcagattgataaaagcaatact cctgggaaaagaciatfaacatgataaaagggtttccttgcagataataactag cg[c/t]gcaccctcctgtgctcagagccctcctgagtataatgacggtagt ggagaatgaatcggcccttgagacagtaataataaaactctgatttggggagc agcggctctctatttttctctctgtgtgggaatgagtgtccaaagcttttactcg gctgataccctttataccctgaaatcagccctcgtgcaactcgtcctcgtataaagc atcacagtgctgcggaggtctaccagctcccaaccatgcccacaaatgtagtct acaggttactgactcctctatgacagtttacaataiga	
POU1F1	D12887	502	0.00%	0.00%	8.33%	<0.01	A/T	Exon 1	T>S	ctgggaaaagaciatfaacatgataaaagggttcttctgcagataataactagc ggcaccctcctgtgctcagagccctcctctgagtataatgacggtagtgaga attgaatcggcccttggagacagtaataataaaactctgatttggggagcagcgg gttctctatttttctctctgtgtgggaatgagtgtccaaagcttttactcggctga t[a/t]cctttatccttgaattgagccctcgtgcaactcgtcctcgtataatgctac acaggtgcggaggtgtaccagctcctcaaccatgcccacaaatgtagtctctac agggtactgactcctatgacagtttacaataigacggggccttaaatctcagaatga atgctttgaaatcttgatagttaa taatctctttgcactcttca ttttaccctc	42
POU1F1	D12889	195	0.72%	0.00%	0.00%	<0.01	C/T	Exon 3	H>H	aaggaaaacaaatgttttggaggatttccataacgactaactacgtccacagtaga gatgaagaagaatgagaatcatctgtacttttttagcaatataataagatatttaacagca ataaagatttgcacaaccagttcttttctgtgtgcttttaacaagcacatacctaatt taattcgtctcactttaaatcatgttggaacttttccagtctctgtatttctggggaat ccatgctattgtgctcttccaccaatttcttccgtgagttcctgcttgaatca gcagctgtgtggggtcctcgtccagagagggctgtgtatagggaggaatccatg actcaagg[t/g/a]tgggtcaggaattataaagacaaggggttaaacctacgtg agtaaacaaaagaataaaatgaaaagaccattgtcattcctcttattctataa gaaagggttttgcctgacttagcccatttctgctctagcc'tgctcagttactaca aggttacccttacatcagctctccgagaagaggtcaaaagtagcttagtagaattg agattattgtctctaccttccagagcagcaaaaccacaaagatagggttaaggg aaaagaagcaggggactgcacaataactaaataagaacaacaacactctctcaga agcatacatcttctatcatgttttctcttaaatgacacctattcctgtgggaatctgagggt tgaactctaacccagagctatgcatgaaactctgttttctta	85

POU1F1	D12889	445	0.72%	0.00%	0.00%	<0.01	A/G	Intron	Non-coding	gcagaaggagatcacatgctacttacttctttgtacttttgaatcataataatggtg gcctattcaaaattcaataaataatagataaaaatgggcacttcaaaactaatgt tgaggtaagtgttgaagagatatttaattaaaaatattgtattttaggccttaaga aattataagggaacaaaatgttttggaggattccataaagactaacactgctccaca gtagagatgaagaatgagaatcatctgtacttttttagcaataataagaga[c]/t taacagcaataaagattgcaaacaccagttcttttctgttgcctttaaacagcaca taactaattraattcgtctactttaattcattggcaaacctttcaagttctctgatttct ggagaatccatgcttattggctctccaccaatttacttttccgcctgagttccgtt gaaatcagcagcgtgtggggctctgcccagaagagcgtgtgtataggggaa atccatgactcaagggtgtgctcaggaattataaagacaaagggttaaacactacc tgtgagtaaacaaagaataaaaatgaaaaagaccatttgcattctctatttctat ataagaaagggtttgcttgcctgacttagccatttctgtctgtagcctgtctcagtact taacaaggcttacttacttccagcttccgaaaggagtcacaaagttagcttagtaga ttacttatatccatgagataatcatttggaaaagatacacaaagggaactaacacgat atacagaaaaagcagcagaaaggatcacatgcttacttacttctttttagcttttga atcataaattgtgtgcttattcaaaattcaataaaaataatagataaaaatgggc acttcaaaactaatgtgtgagtaagttttgaaagagattatttaatttaaaaatattgt attaggctcttaagaaattataaggaaacaaatgttttggaggatttccataacg actaactgcctccagtagagatgaaagattgagaatcatttcta[c]/tjtttttag caataataagagatttaacagcaataaagatttggcaaaccaagcttttttctggt ggccttaacaagcacataccttaatttactgtctactttaattcatttggcaaacctt ttcaagttctgtattctggagaaatccatgcttatttggctcttccaccaatttcttc cggcctgagttctgttgaatcagcagcgtgtgggggtctcttgcaggaagggc tgggtatagggaatccatgactcaagggtgtgtcagggaaatttataaagac aagggttaaaactactgtgagtaaacaaaagaataaaaatgaaaaaacacattt
POU1F1	D12889	467	26.00%	9.52%	66.60%	0.3	G/A	Intron	Non-coding	ttacttatatccatgagataatcatttggaaaagatacacaaagggaactaacacgat atacagaaaaagcagcagaaaggatcacatgcttacttacttctttttagcttttga atcataaattgtgtgcttattcaaaattcaataaaaataatagataaaaatgggc acttcaaaactaatgtgtgagtaagttttgaaagagattatttaatttaaaaatattgt attaggctcttaagaaattataaggaaacaaatgttttggaggatttccataacg actaactgcctccagtagagatgaaagattgagaatcatttcta[c]/tjtttttag caataataagagatttaacagcaataaagatttggcaaaccaagcttttttctggt ggccttaacaagcacataccttaatttactgtctactttaattcatttggcaaacctt ttcaagttctgtattctggagaaatccatgcttatttggctcttccaccaatttcttc cggcctgagttctgttgaatcagcagcgtgtgggggtctcttgcaggaagggc tgggtatagggaatccatgactcaagggtgtgtcagggaaatttataaagac aagggttaaaactactgtgagtaaacaaaagaataaaaatgaaaaaacacattt

POUIF1	D12892	408	unknown	unknown	unknown	unknown	T/A	Exon 6, 3' UTR	Non-coding	tgcacaaacttcactaaacacacaaatttcaccccctatgtccaccocccgc cagcatgtcgtctaaagatgctctggagagacacttggagaaacagataaacct tctctcaagagatcatgaggtggctgaagaaactgaatctggagaaagagta gtaagagtttggtttgcaaccggagcgagagaaacgggtgaaacaaag tctgaatcagagtgatttttctattcttaaggaacatctggagcagataagattttc tattgataatagctttttcccggttcattctctctcctcaacaaaacagaa attactggtgacttaaaatcattttatatacaatagcttttiacagaagctttacttcc actttttt[/a]jaaaaaaaagaaacacaaatttaaattatattatgatttactta aaataattatctcagaagccacattatctattttaagccaaatataattaacagtaata aaatgatctctctgctctccgctctctnctcacacacacgcagacatatagata tgggttataatagttcttcccaacatgtatatagtcttttaacatgttaagtcagtaaa
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[illegible]

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GHSR	U60181	60	3.60%	not available	0.00%	0.04	C/T	Exon	D>D	20

[illegible]

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IGF1	X57025	373					0.02	G/A	exon 2, codon 69	R>R	tcactgctac[tgctaaatcagagcagattagagccctgctggcaatgggaataaagtc ctcaaaaatggaatgtagacatgctctcaacatctccatctctc[tggatttcttttg cttcatttctc[tgctaaccaattcatttcagactttgacttccagaaagcgaatgggaa aaatcagcagcttccaaaccccaatttaataagtgctgcttttggatttctgaaagggtg aagatgacacacacatgctcctcctcgcatctcttactcctgctgctgctgctcactac cttcaccagctc[tgcacagggc[tgagaccggagacgctc[tgcgggggctgagctg tggatgctctcagttcgtggtgtagagacag[g/a]gggtttttatttcaacaagccc acaagggtatggtccacagcagctcggggggcctcagcagagcactcgtgtagatg agtgctgcttccgggagc[tgtagatc[tgaaggggc[tgtagatgtagtctgtagccct caaggcctgccaagtcagctcgtc[tgctcgtggccagcggccacacaccgacatgctc ccaaagaccacagaaaggaaatgtagacatttgaaagaaacgcaatgtaggggtaggctg aaacaagaaactacagtagtaggaagaccctcctgtagggaggtgaaagggtgacat ggcaccggcaggtatccttggctc[tgcacaggttaccctgtttaaactttgggaacacctta ccaaa	69

[illegible]

IGF1	X57025	2350	0.05-0.15	C/T	exon 5, 5' UTR	Non-coding	<p> aaaagctaacagctcaatctctaaacacgtttcaaaaataatgaggagcatttga ttttcaatttgatttgaattcgcatttggtttatgaatacaagaataagtgaaaaga gagaaaggaaaagaaaaggagaaaacaaagagatttctaccagtgaaagg ggaaataatcttcttttag[c/t]actcactgcctctctatgcagtttactacat ctagttaaacctgtttaatactataataattattctatttgaataacacaatga ttctcttttctaggccaataaagggaagtgatcacaatttgaataattataataat atctataaaaaagtcacaaagtattcttctttaaacaacttttacttctttagctgt atatatacttttttaaaaaggtttgtaaaaatatgcttgactagaggttctgtaaaaggc aaaaacttccatcacacaagaataattccatgcctgcacagaagggttagccct agctctctctggaatgtttttatccattcaactgaaaattggtatcaagaaagtcac tggttagtgccttagtccatcatag </p>
IGF1	X57025	2396	0.15-0.50	T/C	exon 5, 5' UTR	Non-coding	<p> aaaagctaacagctcaatctctaaacacgtttcaaaaataatgaggagcatttga ttttcaatttgatttgaattcgcatttggtttatgaatacaagaataagtgaaaaga gagaaaggaaaagaaaaggagaaaacaaagagatttctaccagtgaaagg ggaaataatcttcttttagcactcactgcctctctatgcagtttactacatata gtaaaaacc[t/c]gtttatactataataattattctattcttttgaataacacaatg attctcttttctaggccaataaagggaagtgatcacaatttgaataattataata atatctataaaaaagtcacaaagtattcttctttaaacaacttttacttctttagct gtataatacttttttaaaaagtttgtaaaaatgcttgactagagtttctggttgaagg gcataaaccttccatcacacaagaataattccatgcctgcacagaagggttagcc cctagctctctgtagaatgtttttatccattcaactgaaaattggtatcaagaaagtc cactggttagtgccttagtccatcatag </p>

[illegible]

IGF1	X57025	3276					0.05-0.15	T/C	exon 5, 5' UTR	Non-coding	aaaaataacatcttcagttttctccactgggtccaccctcaagagcagagccag gaaaaaagagactccctggatctctgaaataatgcaaaaagagcccca tttagtggagccagcaatcctgttccagtcacaagatatttaactctcagtcaca ttattgaattgagcaccctcagcatgttgcaatgtttctaatcactatggacagat gtaaaagaactatcacatcttttgcctctgcctgttttcagacacaggttct gtggaataagatactggactctctcccaagatggcactctttttatttctgccc cag[1/c]gtgtaccttttaaaatttccctcacaacaaactttataggcagttctt gcagacttaacatgtttctgtcatagttagtgtgataattcaagagtgctatga ctatttcttcaacttaattatccacagtcacaaaatcccccaaggaggaaagctg aaagatgcaactggccaattattcttttaacttttccacacacataatctcaca ctggattataataaatgaaaataactcatatataccaattcacttatttttttaag aattaaactagaaaacaaaatgtgcaaaccttggaagtcagttgattactatat actacagcagaatgactcagatttcatagaaaaggagcaaccacaaatgtcac atgcaaaaagagggcccatgttgaggccagcaatcctgttcagtcacaag tattttaactctcagtcacacattattgaaatgagccacctcaagcatgttgaat gtttaactactatggacagatgtaaaagaactatacatatttttgcctctgcct gtttccagacatacaggtctgtggataagatactggactctctctcccaagatg gcactctttttatttctgtccctcagtggtacattttaaatttctctcacaacaa actttataggcagctctcagacttaac[a/g]gttttctgtcatagttagtgg ataattcaagagtgctatgacttatttcttcaacttaattctcacacagtcacaaat ccccaaggagggaagctgaaaagatgcaactgccaataatatttcttacttttt ccaacacataatctctccactggattataataaatgaaaataactcatatatac caattcatttttttttaattgaatttaaaactagaaaacaaatgtgcaaacctt ggaaagtcagtgattactatatactacagcagaatgactcagatttcatagaagg agcaaccacaaatgtcacacacaaacttacaagcttgccttcagaattagatgct ttataattcttgaatgaggcaatttcaagatatattgtaaaaggacacagtaaacatt
IGF1	X57025	3340					0.15-0.50	A/G	exon 5, 5' UTR	Non-coding	atgcaaaaagagggcccatgttgaggccagcaatcctgttcagtcacaag tattttaactctcagtcacacattattgaaatgagccacctcaagcatgttgaat gtttaactactatggacagatgtaaaagaactatacatatttttgcctctgcct gtttccagacatacaggtctgtggataagatactggactctctctcccaagatg gcactctttttatttctgtccctcagtggtacattttaaatttctctcacaacaa actttataggcagctctcagacttaac[a/g]gttttctgtcatagttagtgg ataattcaagagtgctatgacttatttcttcaacttaattctcacacagtcacaaat ccccaaggagggaagctgaaaagatgcaactgccaataatatttcttacttttt ccaacacataatctctccactggattataataaatgaaaataactcatatatac caattcatttttttttaattgaatttaaaactagaaaacaaatgtgcaaacctt ggaaagtcagtgattactatatactacagcagaatgactcagatttcatagaagg agcaaccacaaatgtcacacacaaacttacaagcttgccttcagaattagatgct ttataattcttgaatgaggcaatttcaagatatattgtaaaaggacacagtaaacatt

IGF1	X57025	6939								catgaccacacccaactcatagcaaaagtcactctgttaatcccttaactcgtat ttgttggatatttattctgttaccgctctaaacacacacgcaggaggacictga aacctcaagctgtctacttacttattatcttggtaaaagagtaaaagagtgga caaaatatacaaacctttcaaatatcacgcgcttatattcagtttacataaaggcc ccaalacatgcagatcttttggtaaaagagtaaaagagtaaaagagtgga ttacatcatgtatttggcctcatgtattttttacacactttagccaaagtg[c]gata aataaacttiacagacacgtgaatgaatttccctgtctactttgaaaccagaaaaat gactggccattctgtacatctgtctttagtgaaaagcataatttttttaataattct gatgtatttgaattatttcaattcaacttattgagcagagggaatcaatcctaattga cttctaaaaatgtactaaatgaatcattatcttiacatttactgttttaataagcatattt gaaaatgtatggcctagagtgctcataataaaatgggtatattcttctttagttaattcaaa catgaccacacccaactcatagcaaaagtcactctgttaatcccttaactcgtat ttgttggatatttattctgttaccgctctaaacacacacgcaggaggacictga aacctcaagctgtctacttacttattatcttggtaaaagagtaaaagagtgga caaaatatacaaacctttcaaatatcacgcgcttatattcagtttacataaaggcc ccaalacatgcagatcttttggtaaaagagtaaaagagtaaaagagtgga ttacatcatgtatttggcctcatgtattttttacacactttagccaaagtgataaat aaacttiacagacacgtgaatgaatttccctgtctactttgaaaccagaaaaatgac tgccatt[c']gttcatctgtctttagtgaaaagcataltttttttaataattctg atgtatttgaattatttcaattcaactttagcagagggaatcaatcctaattgac ttctaaaaatgtactaaatgaatcattcttiacatttactgttttaataagcatattt aaaatgtatggcctagagtgctcataataaaatgggtatattcttctttagttaattcaaaa
IGF1	X57025	7012								catgaccacacccaactcatagcaaaagtcactctgttaatcccttaactcgtat ttgttggatatttattctgttaccgctctaaacacacacgcaggaggacictga aacctcaagctgtctacttacttattatcttggtaaaagagtaaaagagtgga caaaatatacaaacctttcaaatatcacgcgcttatattcagtttacataaaggcc ccaalacatgcagatcttttggtaaaagagtaaaagagtaaaagagtgga ttacatcatgtatttggcctcatgtattttttacacactttagccaaagtgataaat aaacttiacagacacgtgaatgaatttccctgtctactttgaaaccagaaaaatgac tgccatt[c']gttcatctgtctttagtgaaaagcataltttttttaataattctg atgtatttgaattatttcaattcaactttagcagagggaatcaatcctaattgac ttctaaaaatgtactaaatgaatcattcttiacatttactgttttaataagcatattt aaaatgtatggcctagagtgctcataataaaatgggtatattcttctttagttaattcaaaa

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[illegible]

[illegible]

IGFBP1	M74587	4068	0.00%	2.38%	0.00%	<0.01	G/A	exon 3	V>I	<p>gtgttgagagagtgattggtgagggagagaaatgggtgttctgtttttatctgaaca acttaagacagactaactgcaggtgggaaaaagagggcccgaggggagggcacat cacatgacacccagtcaccaggtcccggtggcccgagatcgtagggccacctgct tctacaaaacctcttccatcagtcattgtctagggcgtgataattcactgtgtctgttag atatgctaattgtcaagttattctttagggagcccgccgaatgaactctacagalg /a]tcgtagagagtttagccaaggcacaggagacatcagggagaaatftcca aatttacc'tggccaactggcaacaaggaaatggattttatcacagcagacaggtggt ggccctggccagtgctgctgctcaggggtgaaagggtccactccaaagtagcacccg ccaagccacgggtcattcattgcaaaagggtccactccaaagtagcacccg agtggtgttattgagccagatcccccctctggggaacctgggaacagctaggtga agaaagccctatgaacaggtcaatatgtcaccaccagaggtgggaaacctggcg ctggaccagggggccctgggggtaaggcctgaggtccatcactcagcaagccaat agctatgggaaggacttctctagggcccccctaacgctggga tcttgggttc atgaacagtgggggcacacacagagacatgtccctctggggatgggctccctga catcaggctatgaagcagacagctgtacacacactgtactgttttaacacacatgg gaagtcattatgcacatgccactggcactgtctctattttatgtatgagaaccag gaggggtgtgagattggcctgcacatcagggcagctgtgttcacagccgggactctt ggcttggctctgcaggtgctgctgctgctgcaaaaaaggggccagctatggctcta ctttccctgtcagctgtcactgtcctgctgctgctgctgttctgttgcaggtga gacatccatggatggagaggcgggactcgtcgtgtg[c/l]gtctacctgggaa tgggaaaggagatcccctgggtctccagagatcagggggagagccccaactggcag atgtattttatgtacaaaaactgaaccagatgaataatgtctgtcacgtgaaat atttaagtatatagttattttatctacttagaacatgtcacattatataatatatgt atatatatataglaactactttttatctccatacataactgtactatataaaggctgttat ttattcacigttaagtttttttttttttacacagtaaaaaactgtactatgttaataactgtc ctatgtcaattgttatatcatgaaacactctcatcatattgtatgtatgaagtaattgcattt ctgctcttccaaaggctccctggcgtctgtgttttaaaaggcagcagaaaaatactgctag</p>
IGFBP1	M74587	5110	1.44%	9.52%	16.60%	<0.01	C/T	exon 4	C>C	<p>atgaacagtgggggcacacacagagacatgtccctctggggatgggctccctga catcaggctatgaagcagacagctgtacacacactgtactgttttaacacacatgg gaagtcattatgcacatgccactggcactgtctctattttatgtatgagaaccag gaggggtgtgagattggcctgcacatcagggcagctgtgttcacagccgggactctt ggcttggctctgcaggtgctgctgctgctgcaaaaaaggggccagctatggctcta ctttccctgtcagctgtcactgtcctgctgctgctgctgttctgttgcaggtga gacatccatggatggagaggcgggactcgtcgtgtg[c/l]gtctacctgggaa tgggaaaggagatcccctgggtctccagagatcagggggagagccccaactggcag atgtattttatgtacaaaaactgaaccagatgaataatgtctgtcacgtgaaat atttaagtatatagttattttatctacttagaacatgtcacattatataatatatgt atatatatataglaactactttttatctccatacataactgtactatataaaggctgttat ttattcacigttaagtttttttttttttacacagtaaaaaactgtactatgttaataactgtc ctatgtcaattgttatatcatgaaacactctcatcatattgtatgtatgaagtaattgcattt ctgctcttccaaaggctccctggcgtctgtgttttaaaaggcagcagaaaaatactgctag</p>

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